

Figure 1. Absorption curve of (1)  $[\text{Cu}(\text{L-ala})_2]$  and circular dichroism curves of (2)  $[\text{Cu}(\text{D-ala})_2]$ , (3)  $[\text{Cu}(\text{L-ala})_2]$ , (4)  $[\text{Cu}(\text{L-ser})_2]$ , (5)  $[\text{Cu}(\text{L-thr})_2] \cdot \text{H}_2\text{O}$ , (6)  $[\text{Cu}(\text{L-val})_2] \cdot \text{H}_2\text{O}$ , and (7)  $[\text{Cu}(\text{L-allothr})_2] \cdot \text{H}_2\text{O}$  in aqueous solutions.

positive shoulder is observed at the longer wave length side (about 830  $\text{m}\mu$ ) of the positive peak. Similar trends are also observed in the curves of  $[\text{Cu}(\text{L-thr})_2]$ ,  $[\text{Cu}(\text{L-val})_2]$ , and  $[\text{Cu}(\text{L-allothr})_2]$ . From Figure 1 it seems likely that the observed broad negative band of  $[\text{Cu}(\text{L-thr})_2]$  or  $[\text{Cu}(\text{L-val})_2]$  is caused by the superposition of two negative CD bands.

From these results it is concluded that the complex  $[\text{Cu}(\text{L-am})_2]$  shows four CD components of the  $d \rightarrow d$  transition which are related to the magnetic dipole allowed transitions under approximately  $C_{2h}$  symmetry, and that the L-configuration of the amino acid determines the signs of these CD components, namely, (+), (+), (-), and (-) from longer to shorter wave lengths. The single ORD inversion observed by Pfeiffer<sup>1</sup> is to be a superposition of four Cotton effects. In this point the present CD method appears to be preferable and more useful.

The CD curves of  $[\text{Cu}(\text{L-prol})_2]$  and  $[\text{Cu}(\text{L-hydprol})_2]$  show considerable difference from the other curves (Figure 2). In the former, this can be attributed to the stereospecific formation of a preferred asymmetric configuration about the nitrogen atom of the proline. Construction of the molecular models of complexes

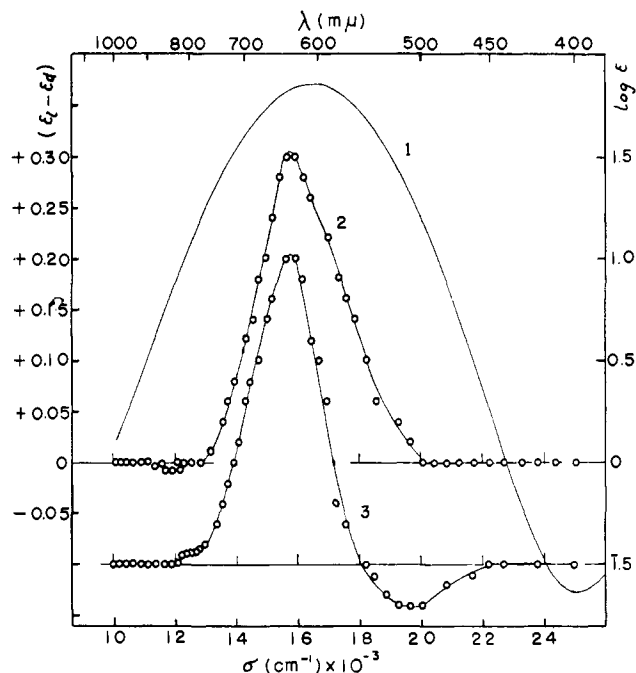


Figure 2. Absorption curve of (1)  $[\text{Cu}(\text{L-prol})_2] \cdot 2\text{H}_2\text{O}$  and circular dichroism curves of (2)  $[\text{Cu}(\text{L-hydprol})_2] \cdot 3\text{H}_2\text{O}$  and (3)  $[\text{Cu}(\text{L-prol})_2] \cdot 2\text{H}_2\text{O}$  in aqueous solutions.

shows that the stereospecificity is perfect and that the nitrogen atom of the coordinated L-proline takes a forced asymmetric configuration and that of the coordinated D-proline the enantiomorphous configuration. This is also supported by X-ray analysis of the  $[\text{Cu}(\text{L-prol})(\text{D-prol})] \cdot 2\text{H}_2\text{O}$  crystal.<sup>5</sup> The vicinal effect from the activated nitrogen atom will be more effective than that from the asymmetric carbon atom, since the nitrogen atom directly attaches to the copper atom but the carbon atom indirectly. The former vicinal effect surpasses the latter and the difference between Figures 1 and 2 is caused.

(5) A. M. Mathieson and H. K. Welsh, *Acta Cryst.*, 5, 599 (1952).

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## Generation of Methylene by Photolysis of Hydrocarbons

Sir:

Methylene sufficiently active to insert into saturated carbon-hydrogen bonds is usually generated by photolysis of ketene<sup>1</sup> and by photolysis<sup>2</sup> or pyrolysis<sup>3</sup> of diazomethane. Photolysis of diazine<sup>4</sup> has also been found to yield a methylene having insertion activity. We now wish to report the generation of methylene by photolysis of hydrocarbons containing a cyclopropyl group adjacent to an aromatic ring. The resulting methylene in hydrocarbon solution exhibits the same indiscriminate insertion into alkane carbon-hydrogen

(1) H. M. Frey and G. B. Kistiakowsky, *J. Am. Chem. Soc.*, 79, 6373 (1957).

(2) W. von E. Doering, R. G. Buttery, R. G. Laughlin, and N. Chaudhuri, *ibid.*, 78, 3224 (1956).

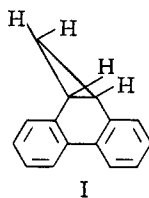
(3) (a) B. S. Rabinovitch and D. W. Setser, *ibid.*, 83, 750 (1961);

(b) D. W. Setser and B. S. Rabinovitch, *Can. J. Chem.*, 40, 1425 (1962).

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bonds as does methylene from diazomethane<sup>2,5</sup> or ketene.<sup>6</sup>

The methylene precursor initially chosen for this study was 9,10-dihydro-9,10-methanophenanthrene (I), molecular models of which indicate the plane of the



cyclopropane ring to be nearly orthogonal to the plane of the aromatic rings. It was synthesized from phenanthrene by reaction with methylene iodide and zinc dust in 1,2-dimethoxyethane<sup>7</sup> and was isolated in 25% yield by extraction of the crude reaction mixture with pentane, removal of most of the unconverted phenanthrene by oxidation with cold aqueous permanganate, and chromatography over silica and nonacidic alumina. The physical and spectral properties of I thus obtained agree in detail with those since reported for this hydrocarbon ("dibenzonorcaradiene"), prepared by cuprous bromide catalyzed homologation of phenanthrene with diazomethane.<sup>8</sup> Further to these data, I is confirmed as C<sub>15</sub>H<sub>12</sub> by mass spectrometry; its infrared spectrum in the region 2000–1667 cm.<sup>-1</sup> (sensitive to differences in ring substitution<sup>9</sup>) is similar to that of 9,10-dihydrophenanthrene, and its near-infrared spectrum (CCl<sub>4</sub>) shows a band at 1.636 μ (overtone for cyclopropane methylene groups<sup>10</sup>). The n.m.r. signals of equal intensity at τ 8.52 and 10.12 (2.2 mole % I, 1.8 mole % TMS in CCl<sub>4</sub>) are assigned, respectively, to the *exo* and *endo* hydrogens of the methylene group; the position of these protons relative to the aromatic rings is such that one expects the *exo* proton resonance to be shifted downfield and the *endo* proton resonance to be shifted upfield from that characteristic of cyclopropane.<sup>11</sup> Also consistent with the structure assigned to I are its relative stability to permanganate and its isomerization to 9-methylphenanthrene over acidic alumina.

A dilute (1–3%) solution of I in cyclohexene was photolyzed in a quartz cell with the unfiltered radiation of a medium-pressure mercury vapor lamp (Hanovia S654A) for 20 hr. Four C<sub>7</sub> hydrocarbons were formed, identified by the retention volumes and infrared spectra of the g.l.c. fractions as 4-, 3-, and 1-methylcyclohexenes and norcarane. These products and their ratios were the same as those produced by photolysis of diazomethane in cyclohexene.<sup>2</sup> Similarly, cycloheptatriene and toluene were formed by photolysis of I in benzene. The cycloheptatriene–toluene ratio was 1.0 rather than 3.7 as observed for diazomethane<sup>12</sup>; the

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(9) C. W. Young, R. B. DuVall, and N. Wright, *Anal. Chem.*, **23**, 709 (1951).

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lower ratio in the case of I is consistent with the finding that cycloheptatriene was photoisomerized under these conditions to toluene and bicyclo[3.2.0]hepta-2,6-diene.<sup>13</sup> Both with cyclohexene and with benzene as solvent the nonvolatile residue was largely (90%) phenanthrene. Photolysis of I thus produces phenanthrene and methylene, the reactivity of the latter being comparable to that for methylene from diazomethane.

The stereochemical behavior of the methylene thereby generated was examined by photolysis of solutions of I in *cis*- and *trans*-4-methylpentene-2. In each case, the products were identical with those obtained by photolysis of diazomethane in the olefin. Further, no *trans*-cyclopropane was found in the product from the *cis*-olefin nor *cis*-cyclopropane from the *trans*-olefin. These results show that methylene from I is stereospecific in its addition to olefins, as is methylene from diazomethane.<sup>14,15</sup>

In order to compare the insertion reactivity of this methylene with that from photolysis of diazomethane, alkane solutions of I were irradiated as above and the products were analyzed by capillary g.l.c.<sup>16</sup> (Table I). Carbon–hydrogen insertion of methylene occurred in each case to give the expected products. Furthermore, the observed product distributions are in good agreement with those calculated for random insertion and those established for methylene from diazomethane.<sup>2,5</sup>

Because of its structural similarity to I, phenylcyclopropane (II) was also examined as a possible methylene precursor. It was readily prepared from styrene *via* the zinc–methylene iodide reaction in 1,2-dimethoxyethane. The identity of II thus obtained was confirmed spectroscopically (mass, ultraviolet, infrared, near-infrared, and n.m.r.). Hydrocarbon solutions of II were irradiated and analyzed as above. The observed products were those to be expected from reaction of methylene with the respective solvents. Cyclohexene gave the three methylcyclohexenes and norcarane, benzene yielded cycloheptatriene and toluene, and alkanes produced only those products expected from C–H insertion. The data of Table I show that insertion by this methylene also occurs randomly. Although no styrene was found in the photolyzed solutions, polymer appeared on the walls of the cell, and control experiments showed that styrene is polymerized under the conditions of the photolysis.

With reference to the "norcaradiene" structure of I and the cycloheptatriene–norcaradiene problem,<sup>17</sup> the possibility of generating methylene from cycloheptatriene was also investigated. Hydrocarbon solutions of cycloheptatriene were irradiated as above. Careful examination of the products gave no evidence for production of methylene; in each experiment, the above-mentioned photoisomerization was the only reaction observed.

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**Table I.** Comparative Distribution of Methylene Insertion Products

Substrate	Product	% calcd.	% obsd.		
			From I	From II	From CH <sub>2</sub> N <sub>2</sub> <sup>a</sup>
Pentane	2-MeC <sub>5</sub>	33.3	34		34
	3-MeC <sub>5</sub>	16.7	17		17
	C <sub>5</sub>	50.0	49		49
3-Methylpentane	3,3-Me <sub>2</sub> C <sub>5</sub>	7.1		7	7
	2,3-Me <sub>2</sub> C <sub>5</sub>	28.6		30	31
	3-MeC <sub>6</sub>	42.9		43	44
	3-EtC <sub>5</sub>	21.4		20	18
2,4-Dimethylpentane	2,2,4-Me <sub>3</sub> C <sub>5</sub>	12.5		10	10
	2,4-Me <sub>2</sub> C <sub>6</sub>	75.0		77	78
	2,3,4-Me <sub>3</sub> C <sub>5</sub>	12.5		13	12
2,4-Dimethylhexane	2,2,4-Me <sub>3</sub> C <sub>6</sub>	5.6	6		5
	[2,4,4-Me <sub>3</sub> C <sub>6</sub> <sup>b</sup>	16.7	17		16
	2,3,5-Me <sub>3</sub> C <sub>6</sub> ]				
	2,4-Me <sub>2</sub> C <sub>7</sub>	16.7	18		19
	2-Me-4-EtC <sub>6</sub>	16.7	16		16
	3,5-Me <sub>2</sub> C <sub>7</sub>	33.3	34		35
	2,3,4-Me <sub>3</sub> C <sub>6</sub>	11.1	9		10
2,2,4-Trimethylpentane	2,2,4,4-Me <sub>4</sub> C <sub>6</sub>	5.6	4	5	4
	2,2,4-Me <sub>3</sub> C <sub>6</sub>	33.3	37	36	35
	2,4,4-Me <sub>3</sub> C <sub>6</sub>	50.0	49	49	51
	2,2,3,4-Me <sub>4</sub> C <sub>5</sub>	11.1	10	10	10
2,3,4-Trimethylpentane	2,2,3,4-Me <sub>4</sub> C <sub>5</sub>	11.1	10	11	10
	2,4-Me <sub>2</sub> -3-EtC <sub>5</sub>	16.7	14	16	16
	2,3,4-Me <sub>3</sub> C <sub>6</sub>	66.7	70	67	69
	2,3,3,4-Me <sub>4</sub> C <sub>5</sub>	5.6	6	6	5

<sup>a</sup> CH<sub>2</sub>N<sub>2</sub> data for pentane taken from ref. 2; other CH<sub>2</sub>N<sub>2</sub> data taken from ref. 5 or present study. <sup>b</sup> Incomplete resolution.

Apart from the theoretical significance of these new precursors, they constitute a convenient, shelf-stable source of active methylene. The hydrocarbon precursors are thus particularly suitable for small-scale synthesis<sup>16</sup> and C<sup>14</sup> labeling<sup>18</sup> *via* methylene insertion and should facilitate application of these techniques to substrates which undergo dark reactions with the functional methylene precursors.

**Acknowledgment.** We are grateful to Mr. L. M. Taylor for experimental assistance and to Dr. F. D. Mango for helpful comments.

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(19) Mesa College, Grand Junction, Colo.

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## An Efficient Synthesis of Estrone and 19-Norsteroids from Cholesterol

Sir:

The increasing medical importance of 19-norsteroids, particularly as prostagens<sup>1</sup> for ovulation control, has generated intensive research to find more economical routes, either by direct partial or total synthesis or indirectly *via* estrone, to this class of compounds.<sup>2</sup>

(1) G. Pincus and A. P. Merrill in "Control of Ovulation," C. A. Villee, Ed., Pergamon Press, New York, N. Y., 1961, p. 37.

In our previous communication<sup>3</sup> we described the feasibility of the cleavage of the sterol side chains by microbial means, thus providing an alternate source of starting materials for the preparation of steroid hormones. It was shown that 19-hydroxycholest-4-en-3-one and 19-hydroxysitost-4-en-3-one could be converted into estrone by microorganisms. As an extension of this finding, we herein report an improved and highly efficient route for the preparation of estrone and 6,19-oxidoandrost-4-ene-3,17-dione (I), a key intermediate for the synthesis of 19-norsteroids<sup>4</sup> from cholesterol.

Previous studies have shown that in general most bacteria contain enzyme systems which are capable of (1) cleaving acetoxy functions at C-3<sup>5</sup>; (2) oxidation of hydroxyl groups at C-3 to ketones;<sup>6</sup> (3) isomerization of the double bond<sup>7</sup> ( $\Delta^{5,6}$  to  $\Delta^{4,5}$ ); (4) introduction of a 1,2-double bond<sup>8,9</sup>; (5) cleavage of the cholesterol side chain in a series of reactions which eventually lead to a 17-ketone function.<sup>3,10</sup> When these isolated facts are brought into focus, it appears to us that an ideal substrate for the microbial conversion to estrone would be 3 $\beta$ -acetoxy-19-hydroxycholest-5-ene<sup>4</sup> (II) since this compound could be conveniently prepared from cholesterol acetate in three chemical steps. Also, by taking advantage of all the enzymes produced by the microorganism, a shorter synthesis to estrone could be realized.

In a typical experiment, 1.2 g. of II was incubated with CSD-10<sup>11</sup> for 96 hr. in Difco nutrient broth; 527 mg. of estrone (72%), m.p. 257–260°, was obtained (identity with an authentic sample established by mixture melting point and infrared spectrum).

We have previously shown that I could be converted into 6,19-oxido-9 $\alpha$ -hydroxyandrost-4-ene-3,17-dione (III) by the organism *Nocardia restrictus* (ATCC 14887).<sup>12</sup> However, the presence of the 6,19-oxido function in the molecule apparently blocked the introduction of the 1,2-double bond by the microorganism, resulting in the accumulation of the product, III. On the basis of this observation, it occurred to us initially that 6,19-oxidocholest-4-en-3-one (IV) should be a substrate for microbial conversion, but the major product of this microbial transformation could be either I or III. When 900 mg. of IV was incubated with CSD-10 for 70 hr., 375 mg. (57%) of I was obtained, m.p. 182–185° (identical with an authentic specimen with respect to mixture melting point and infrared spectrum), along with 150 mg. of a mixture consisting mainly of III, m.p. 263–266°, and a small amount of a dihydro derivative of III.

In an attempt to devise a more efficient synthesis of I, by similar lines of reasoning, we predicted that 3 $\beta$ -acetoxy-5-chloro-6,19-oxidocholestane<sup>4</sup> (V) would be an ideal substrate for microbial transformation into I; V

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